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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,310	10/20/2008	Alexei M. Voloshin	STAN-353	6761

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
05/06/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,310	VOLOSHIN ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,12,13 and 15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12,13,15,16 and 18-24* is/are rejected.

7)☒ Claim(s) *2,3,5,6 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/1/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on February 1, 2011.

Preliminary Remark

Claims 4, 7-11, and 14 are canceled.

Claims 22-24 are new.

Information Disclosure Statement

The IDS received on February 1, 2011 is proper and is being considered by the Examiner. The IDS was received with the fee submission under 35 CFR 1.17(p).

Claim Rejections - 35 USC § 112

The rejection of claims 6, 12, 15, and 21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, for reasons set forth in the Office Action mailed on October 1, 2010 is withdrawn in view of the Amendment received on February 1, 2011.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12, 15, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 15, and 21 are indefinite because it is unclear what antifoam agents are covered by the metes and bounds of the claims. Claims as amended recite that antifoam agent is a block copolymer "surfactant with low ethylene oxide content..." Such recitation confuses the metes and

bounds of the claim because it is unclear what is meant by a block copolymer with ethylene oxide "content." (does it mean that it has ethylene oxide or not?) Also, what is meant by "low" ethylene oxide content? Can one distinguish an antifoam agent having a moderate and high ethylene oxide content which is not embraced by the relative language "low ethylene oxide content?

Such vague and relative language renders the claims indefinite therefore.

Claim 15 refers to claim 13 as the "reaction mixture."

Claim 13, however, is drawn to a method. Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 12, 13, 15, 16, and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rashtchian et al. (US 2005/0123924 A1, published June 9, 2005, priority August 5, 2002) in view of Lipshutz et al. (U.S. Patent No. 5,856,174, issued January 5, 1999).

Rashtchian et al. disclose a method of *in vitro* transcription of mRNA ("effect of anti foam agents on enzymatic reactions for synthesis of RNA was studied by in vitro transcription...", section [0098]), the method comprising the steps of:

synthesizing said mRNA in a cell-free reaction mixture ("double strand cDNA could be used as a template for *in vitro* transcription using T7 RNA polymerase ...", section [0098]), comprising an anti foam agent at a concentration of at least 0.0007%, and not more than 0.007% by weight,

wherein the antifoam agent is other than a detergent ("inclusion of antifoam in transcription did not interfere with T7 RNA polymerase activity and in vitro transcription of RNA. In addition presence of 2x antifoam resulted in faster kinetics of RNA synthesis and at the 2-hour time point there was a 10% increase in the amount of RNA synthesized", section [0102]; "1 x concentration: 0.005% Sigma O-30 and 0.001% Dow 1520-US", section [100]; "2x concentration: 0.01% Sigma O-30 and 0.002% Dow 1520-US", section [0101]).

With regard to claims 12, 15, and 21, since the anti foam agent of Rashtchian et al. achieves the same result; it is deemed that the agent of Rashtchian et al. also meets the limitation.

Rashtchian et al. do not explicitly disclose that a cell extract, monomers for the mRNA ... and cofactors and other reagents are necessary for the synthesis is used (claim 13), and consequently do not explicitly such a reaction mixture (claim 16).

Rashtchian et al. do not explicitly disclose that the synthesizing is conducted in a mixture volume of at least about 15μl, or 1000 μl (claim 18), a reactor (claim 19), a bubble reactor (claim 20).

Lipshutz et al. disclose a well known practice of using a reactor for transcription reaction for generating IVT (column 32, lines 21-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Rashtchian et al. with the teachings of Lipshutz et al., thereby arriving at the invention as claimed for the following reasons.

Rashtchian et al. already disclose that the addition of anti foaming agent resulted in the increased production of RNA synthesis. While the artisans were not explicit in disclosing that the reaction take place in a certain volume of a reaction mixture, having been provided with the teachings that *in vitro* transcription reaction yield increases with the use of anti foaming agent, one of

ordinary skill in the art would have been capable of determining what volume of mixture to conduct the reaction in, as such simply involves routine optimization.

While Rashtchian et al. are not explicit in reciting every ingredient required in *in vitro* transcription, such would have been an obvious knowledge to one of ordinary skill in the art as the transcription reaction conducted *in vitro* had been around for decades. Therefore, while Rashtchian et al. did not explicitly disclose that certain monomers, enzymes, buffers, co-factors, etc. should be present in their method or in a mixture of the method, such knowledge would have been already attained by the ordinarily skilled artisan. As to packaging the reaction reagents into a kit, such would have been an obvious thing to for the benefit of providing pre-purified, pre-weighed reagents, with instructions streamlined for a particular use.

Therefore, the invention as claimed is deemed *prima facie* obvious over the cited references.

Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rashtchian et al. (US 2005/0123924 A1, published June 9, 2005, priority August 5, 2002) in view of Lipshutz et al. (U.S. Patent No. 5,856,174, issued January 5, 1999) as applied to claims 1, 12, 13, 15, 16, and 18-21 above, and further in view of Wachala et al. (U.S. Patent No. 3,990,905, issued November 9, 1976).

The teachings of Rashtchian et al. and Lipshutz et al. have already been discussed above.

Rashtchian et al. and Lishutz et al. do not explicitly disclose all possible anti foaming agents, such as those recited in claims 22-24.

Wachala et al. disclose an anti foaming agent used in food processing, said agent being polyethylene glycol esters (column 4, lines 36-65).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Rashtchian et al. and Lipshutz et al. with the teachings of Wachala et al., thereby arriving at the invention as claimed.

The motivation to combine the teaching of Wachala et al. is predominantly provided for by Rashtchian et al. who expressly disclose that the use of anti foaming agent in an *in vitro* transcription reaction resulted in higher production of RNAs. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings of Rashchian et al. with the teachings of other known anti foaming agents, for the same predictable desired outcome of increasing RNA yield in an *in vitro* transcription reaction.

In KSR (citation omitted), the Supreme Court particularly emphasized "the need for caution in granting a patent based on the combination of elements found in the prior art,"Id. at ___, 82 USPQ2d at 1395, and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at ___, 82 USPQ2d at 1395.

Therefore, the invention as claimed is deemed *prima facie* obvious over the cited references.

Conclusion

The prior art does not teach or suggest for a method of *in vitro* translation of polypeptides using a non-detergent anti-foaming agent at concentration range of 0.00007% to 0.007% by weight.

The instant specification discloses that the success of using antifoam in a cell-free synthesis is unexpected as the presence of anti-foam agent in a cell-free environment would be expected to

interfere with **protein synthesis** and folding as the catalysts and nascent products would not be protected within a cell:

> For *in vitro* synthesis, the hydrophobic components of antifoam would be expected to interfere with protein synthesis and folding, since the catalysts and nascent products are not protected within a cell as they are when proteins are expressed *in vivo*, e.g., by conventional recombinant expression methods. The results provided herein are therefore unexpected." (page 4)

While Rashtchian et al. disclose that the use of anti foaming agent in an *in vitro* transcription reaction results in an increased RNA yield, it is deemed that whether the use of anti foaming agent in an *in vitro* (or cell free) translation of protein would also be non-negatively impacted, as the elements required in translation process would not be shielded from the anti foaming agent in such a process.

In deed, Zhang et al. (Journal of Biotechnology, 1992, vol. 25, pages 289-306; IDS ref), a related art of generating monoclonal antibodies in cells wherein anti an foaming agent is used, disclose the desire to protect the cells contents within the cell boundaries via use of anti foaming agent:

> "Foam formation and the subsequent cell damage/losses in the foam layer were found to be major problems affecting cell growth and monoclonal antibody (MAb) production in stirred and sparged bioreactors for both serum-supplemented and serum-free media. Surfactants in the culture media had a profound effect on cell growth by changing both the properties of bubbles and the properties of foam formed. Comparable cell growth and MAb production in sparged bioreactors and in stirred and surface-aerated control cultures were observed only in Pluronic F-68 containing culture media … Pluronic F-68 provided protective effect to cells but not to the medium …" (Abstract)

While Zhang et al.'s disclosure does not have anything to do with reactions involving *in vitro*, the artisans do demonstrate that the art's desire to retain cell's contents for conducting cell reactions (*i.e.,* antibody production) within the cell boundaries, away from contact with an anti foaming agent (Pluronic F-68). Therefore, it is deemed that one of ordinary skill in the art would not have

expected that a protein translation process in an *in vitro* reaction setting would have proceeded without hindrance in the presence of an anti foaming agent.

Accordingly, claims 2-6 and 17 are free of prior art, but objected to for being dependent on a rejected base claim.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 6:00 a.m. to 2:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system,

see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
5/5/2011

/YJK/